LUDWIG
CANCER
RESEARCH

2018 RESEARCH HIGHLIGHTS

LIFE-CHANGING SCIENCE

WELCOME

Ludwig Cancer Research has many gifted scientists who have many interesting findings to share. Every year we pick out a few fascinating discoveries reported by Ludwig researchers in the previous year and tell the stories of how they came about. Not the short version, of the discovery itself, but the long one, of the journey of scientific inquiry that led to each finding and the lives, careers and fascinations of the scientists who led the effort. We highlight in this report a cross-section of Ludwig's life-changing science that illustrates how we're pursuing our mission to advance cancer research and care.

One theme that leaps out in this report is the importance of teachers—the sort who turn science into poetry and transform students into independent investigators. These teachers go the extra mile to engage and excite their students with the power of the scientific method and its ability to illuminate the mysteries of nature. They are mentors who stick out their necks for young scientists, take a chance on them and help them fulfill their scientific aspirations. Many of the scientists we profile express an immense gratitude for their teachers, and in turn become mentors and take genuine pride in the young scientists they themselves have trained.

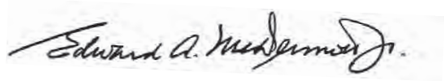
The profiles also bear out the global scope of our effort to conquer cancer. In establishing the Ludwig Institute for Cancer Research, Daniel K. Ludwig argued that "the rare vision and ability needed in the battle against cancer are not limited by frontiers, and the scientists who possess these gifts must be sought wherever they are to be found." You will notice that many of the researchers profiled here are immigrants and world travelers. Others made their contributions while remaining in their native countries. Together, these researchers represent an endeavor that transcends country, creed or color to harness talent from all corners of the world to a common and humane cause.

Ludwig is proud to be a leader of this cause, and we hope you enjoy this small sampling of our contributions.

Happy reading!

Sincerely,

Ed and Chi



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JOHANNA **JOYCE**

LUDWIG **LAUSANNE**

Photo by Gilles Weber

THE TUMOR ECOLOGIST

Her ongoing investigation of how noncancerous cells in the microenvironment of tumors contribute to malignant growth, drug resistance and metastasis is also revealing how such relationships might be disrupted to treat cancer.

Johanna Joyce was puzzled. The cause of her befuddlement: positive results from an experiment in a mouse model of glioma, an aggressive brain cancer.

The year was 2012, and it was already known that macrophages—immune cells that ordinarily gobble up cancer cells and infectious agents—often turn traitor, multiply within tumors and drive cancer progression. Joyce, who was at Memorial Sloan Kettering Cancer Center (MSK) at the time, wanted to see what would happen if such turncoat macrophages in gliomas were targeted with an inhibitor of the CSF-1 receptor (CSF-1R), whose activity is normally essential to their survival.

"The results were striking," says Joyce, who joined the Ludwig Branch in Lausanne, Switzerland, in 2016, where she is a Member. "Even after treatment of just one week, we saw a pretty dramatic regression of the tumors." But what puzzled her was that the tumors were still teeming with macrophages.

As Joyce and her team reported in *Nature Medicine* in 2013, the glioma cells were producing factors that helped macrophages survive the therapy. But the loss of the receptors' signal, rather than killing the tumor-associated macrophages (TAMs), had "reeducated" them, altering their gene expression programs to convert them back into cancer cell gourmands.

That study, with its scientific and therapeutic implications, put the Joyce laboratory on the map of tumor biology. In the years since, she and her lab have continued to expose the intricate interplay between cancer cells and a motley crew of noncancerous cells in the tumor microenvironment. In 2017, she and her team at Ludwig Lausanne reported in *Oncogene* how macrophages help gliomas resist targeted drug therapy and how such resistance might be overcome with CSF-1R inhibition. Another Joyce lab publication in *Cell Reports* described a similar macrophage role in chemotherapy resistance. Finally, a

"It was teaching as teaching should be done. They taught us how to think about science through stories of how the discoveries happened. That made it so fascinating that you just wanted to learn more and more."

Nature Cell Biology publication elucidated how obesity, through its effects on another type of immune cell, the neutrophil, drives the spread of breast tumors to the lungs.

Student days

When Joyce was 14 years old, her parents moved her and her four younger siblings from London to a farm they bought outside Dublin. Joyce's omnivorous appetite for science intensified under the influence of the teachers at her new school—particularly, she recalls, an enthusiastic chemistry instructor named Mr. Bennett. After finishing school, she enrolled in an honors program in the natural sciences at Trinity College, in Dublin, where she ultimately focused on genetics. "I thought the inherent logic of it was quite beautiful," she says.

The professors of genetics at Trinity, she says, were the best teachers she ever had. "They instilled in us an absolute love for genetics of all types," she says. "It was teaching as teaching should be done. They taught us how to think about science through stories of how the discoveries happened. That made it so fascinating that you just wanted to learn more and more, and enjoyed going to the classes so much. It's something I try, to the extent I can, to bring into how I teach my own students."

Joyce's honors thesis at Trinity, on genomic imprinting—the regulation of a subset of genes depending on which parent they're inherited from—led directly to doctoral research in clinical genetics at Cambridge University, in the laboratory of Paul Schofield. There she explored how the faulty regulation of imprinted genes causes Beckwith-Wiedemann syndrome, which predisposes children to cancer.

Into the microenvironment

An urge to go beyond cancer genetics and plunge deeper into the multicellular complexity of cancer took Joyce to Douglas Hanahan's laboratory, then at the University of California, San Francisco, where she started her postdoctoral studies in 1999. Collaborating with the chemical biologist Matthew Bogyo, Joyce explored how cathepsins—a family of protein-snipping molecular scissors—participate in multiple aspects of pancreatic cancer progression.

Their studies also revealed that immune cells are notably avid expressers of cathepsins. "That early result," says Joyce, "ultimately led me to focus on the roles of TAMs in cancer initiation, progression, invasion and response to therapy, and so it set the stage for the whole program that I developed in my own lab in New York and that continues here in Lausanne."

Photo by Eric Déroze

After joining MSK in 2004, Joyce expanded her studies to investigate TAMs in breast cancer and, later, in gliomas, ultimately leading to the *Nature Medicine* paper on CSF-1R inhibition and TAM reprogramming.

"That was a different way of thinking about targeting the tumor microenvironment," says Joyce. "You don't necessarily want to deplete these and other immune cells in cancers because they have critical housekeeping functions. But by re-educating them so that they can again execute those functions we could potentially get better therapeutic outcomes."

Resolving resistance

But would the effect last? Or would gliomas, among the wiliest of malignancies, develop resistance?

In a 2016 paper published in *Science* after Joyce joined Ludwig Lausanne, she and her colleagues addressed those questions. They found that after prolonged treatment, about half of the gliomas in mice became resistant to the CSF-1R inhibitor and every tumor that recurred did so in the context of a scar. "We identified a prominent and quite complex resistance mechanism involving many different cell types within these treated lesions that ultimately led to the reemergence of glioma cell proliferation and invasion," says Joyce.

Prolonged treatment with the anti-CSF-1R drug in the context of recurrent disease prompted macrophages to adopt a wound healing response. That includes secreting growth factors such as insulin-like growth factor-1 (IGF-1), which they do in response to another factor (interleukin-4) produced by infiltrating T cells of the immune system. IGF-1, for its part, activates a signaling pathway in the cancer cells that drives their growth—a pathway mediated by a protein named PI-3 kinase (PI3K). The CSF-1R resistance, the researchers showed, could be overcome with drugs that block the receptor for IGF-1 or PI3K activity. Combining either with

Photo by Gilles Weber

CSF-1R blockade extended survival in a mouse model.

Restorative interventions

Like many other cancers, gliomas are driven in large part by the unbridled activity of a diverse and ubiquitous clan of signaling enzymes known as tyrosine kinases. But drugs that inhibit various kinases have had little or no effect on gliomas. Joyce and her team noticed, however, that tyrosine kinase inhibitors were nonetheless very effective in killing glioma cells in culture. "Whenever you see something like that, it grabs your attention," says Joyce.

It suggested, for one thing, that the observed drug resistance might stem from the tumor microenvironment. In 2017, Joyce and her team reported in *Oncogene* that inhibiting CSF-1R with a drug could restore sensitivity to other tyrosine kinase inhibitors in mouse models. In this case, they showed, the reprogramming of TAMs by CSF-1R inhibition was directly involved in making gliomas susceptible to the cancer cell-targeted inhibitors.

"We used the knowledge we had of macrophages and of CSF-1R signaling and inhibition to overcome this microenvironment-mediated resistance to therapy—something we and others are finding is extremely important to the efficacy of multiple therapies in many different cancers," says Joyce.

Indeed, she and her group had already shown in 2011 that treating breast cancer with Taxol tends to boost TAM numbers, which drives resistance to chemotherapy. In 2017, her laboratory demonstrated in a *Cell Reports* paper that macrophages also secrete factors that interfere directly with Taxol's effects on cancer cells—which is to force an extended arrest during cell division that prompts their suicide. TAMs, Joyce and her colleagues found, shortened the duration of the mitotic arrest induced by Taxol. They also showed that inhibiting a signaling pathway involved in this interference, mediated by a protein named MEK, could restore sensitivity to Taxol.

Prep work

While at MSK, Joyce's team had held joint meetings with the laboratory of Andrew Dannenberg, a colleague at Weill Cornell Medical College in New York. Dannenberg and his team were interested in the link between obesity and different cancers, including breast cancer; Joyce and her team were particularly intrigued by the effects of obesity on systemic inflammation and potential connections to metastasis.

With a shared expertise in TAMs, the researchers looked at the effects of obesity on these cells first. But they quickly noticed that neutrophils—another type of immune cell—were more intimately linked to inflammation in the obese. "We found that in the normal lung, outside of the context of cancer, there was already a profound accumulation of neutrophils," says Joyce. This was evident in obese mice as well as in blood samples from obese women.

In 2017, Joyce and her colleagues reported in *Nature Cell Biology* that neutrophils accumulate in the lungs of obese mice and that the effect is exacerbated in the presence of a breast tumor. Neutrophils, it appeared, prepare a niche for colonizing breast cancer cells—which would explain why obese women with breast cancer have an increased risk of developing lung metastases and a typically worse prognosis.

The increased metastasis is dependent on the immune factors interleukin-5 and GM-CSF, and blocking those factors pharmacologically inhibited the effect in mice. Intriguingly, and potentially important from a public health perspective, they found neutrophil migration and the enhanced metastasis could also be reversed by weight loss—at least in mice.

Such microenvironmental discoveries will be incorporated into the ambitious cancer immunotherapy program now underway at Ludwig Lausanne. Joyce is already working with neuro-oncologists and surgeons at the Lausanne University Hospital (CHUV) to that end. "We have established some fantastic collaborations with CHUV to perform immune cell landscaping in every brain malignancy that is operated on in the hospital," she says, "and in parallel we are preparing to use our preclinical models to try to develop novel immune therapies within the brain."

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Meanwhile, Joyce's breakthroughs have generated intriguing opportunities—including in a team that won a £20 million Cancer Research UK Grand Challenge award in 2017. Led by Greg Hannon of Cambridge, the international team will construct an immersive, 3D version of breast tumors that can be studied through virtual reality. "This Grand Challenge project is completely unbiased in terms of the cells we're looking at," says Joyce. "We want to explore all of it, to tackle that complexity head on."

Joyce, in other words, plans to keep doing what she's been doing all along.